ORIGINAL ARTICLE

Intraoperative Low-Dose Ketamine Infusion Reduces Acute Postoperative Pain Following Total Knee Replacement Surgery: A Prospective, Randomized Double-Blind Placebo-Controlled Trial

Pelin Cengiz, Derya Gokcinar, Isil Karabeyoglu, Hulya Topcu, Gizem Selen Cicek and Nermin Gogus

Abstract

Objective: To evaluate the effect of intraoperative low-dose ketamine with general anesthesia on postoperative pain after total knee replacement surgery.

Study Design: A randomized, double-blind comparative study.

Place and Duration of Study: Ankara Numune Training and Research Hospital, Turkey, from January and June 2011.

Methodology: Sixty adults undergoing total knee arthroplasty were enrolled in this study. The patients were randomly allocated into two groups of equal size to receive either racemic ketamine infusion (6 µg/kg/minute) or the same volume of saline. A visual analogue scale (VAS) was used to measure each patient's level of pain at 1, 3, 6, 12, and 24 hours after surgery. Time to first analgesic request, postoperative morphine consumption and the incidence of side effects were also recorded.

Results: Low-dose ketamine infusion prolonged the time to first analgesic request. It also reduced postoperative cumulative morphine consumption at 1, 3, 6, 12, and 24 hours postsurgery ($p < 0.001$). Postoperative VAS scores were also significantly lower in the ketamine group than placebo, at all observation times. Incidences of side effects were similar in both study groups.

Conclusion: Intraoperative continuous low-dose ketamine infusion reduced pain and postoperative analgesic consumption without affecting the incidence of side effects.

Key Words: *Acute postoperative pain. Preventive analgesia. Ketamine. Postoperative analgesic consumption. Knee replacement surgery.*

INTRODUCTION

The magnitude of postoperative pain differs due to type of surgery. Orthopedic patients suffer from severe immediate postoperative pain more than laparotomy patients and they require more analgesia.[1] A clinical practice guideline, based on the systematic review of published studies about the management of post-operative pain after total knee arthroplasty, was reported by Korean Knee Society. In this guideline, pre-emptive analgesics, multimodal analgesics, epidural analgesia, femoral nerve block, periarticular injection, patient-controlled analgesia, oral analgesics, and patient education are preferential to control postoperative pain after total knee arthroplasty.[2]

Tissue reaction to the surgical procedure leads to release of inflammatory mediators, which stimulates peripheral nociceptors. Nociceptive information transduced and transmitted to the CNS.[3] Extreme noxious input may produce central sensitization and pain hypersensitivity.[4] Particularly, constant release of inflammatory mediators in the periphery triggers latent nociceptors.[5] Pre-emptive analgesia via precluding central sensitization may diminish acute postoperative pain.[6] Ketamine attenuates central sensitization by inhibition of N-methyl-D-aspartate (NMDA) amino acid receptors.[7] While most studies indicate that intraoperative ketamine has postoperative analgesic activity,[8] others failed to prove this.[9] Ketamine was also found effective when combined with various forms of anesthesia, and reduced pain following different types of surgery. It also reduced postoperative requirements for narcotics and other analgesics, following abdominal surgery.[10] Ketamine also had a morphine-sparing effect after total hip arthroplasty, even when morphine was combined with a systemic multimodal analgesic regimen that included paracetamol and non-steroidal anti-inflammatory drugs.[11]

In particular, Fu *et al*. reported that infusion of ketamine throughout abdominal surgery was more effective in decreasing the need for postoperative opioids than post-wound closure administration of ketamine.[12] Perrin and Purcell recently conducted a study on intraoperative ketamine infusion during knee arthroplasty, and reported that more patients were pain-free in the ketamine group than in the placebo group.[13] However, their study

Department of Anesthesiology, Ankara Numune Training and Research Hospital, Ankara, Turkey.

Correspondence: Dr. Derya Gokcinar, Department of Anesthesiology, Ankara Numune Training and Research Hospital, Talatpasa Bulvari, No. 5, Altindag, Ankara, Turkey. E-mail: dgokcinar@yahoo.com

Received: October 10, 2012; Accepted: November 12, 2013.

included few patients as well as their anesthesia method was both general and spinal anesthesia. Information is limited on the use of intraoperative low-dose ketamine infusion with general anesthesia only.

The present study was conducted to evaluate the effect of continuous intraoperative low-dose ketamine infusion combined with general anesthesia on pain following total knee replacement surgery.

METHODOLOGY

This study was a prospective, randomized, double-blind, comparative, placebo-controlled study of the efficacy of continuous intraoperative low-dose ketamine infusion for postoperative pain following total knee replacement surgery. Ethical approval for this study was provided by the Clinic Research Ethical Committee of The Turkish Ministry of Health, Ankara [#9-05]. The study was conducted between January to June 2011 at Numune Training and Research Hospital, Ankara, Turkey.

Consecutive patients aged 18 - 65 years, ASA grade I, II or III, who were scheduled for total knee arthroplasty surgery under general anesthesia were inducted. Patients were excluded if they had an allergy to ketamine, a severe cardiovascular disorder (ejection fraction < 30%), renal insufficiency (creatinine clearance < 30 mL/min), an inability to understand the use of patient-controlled analgesia (PCA), a rejection to receive general anesthesia, or a willingness to receive regional anesthesia.

All patients signed written informed consent. Pre-operatively, all participants received instructions on the use of the PCA device and rating pain on the visual analog scale (VAS; ranging from 0 cm = no pain to 10 cm = greatest level of intolerable pain).

No premedication was prescribed to avoid effects on the outcomes of the study. Routine monitors were attached in the surgical suite. Anesthetic protocol was standardized for all patients. Anesthesia was induced with intravenous (IV) propofol (2 mg/kg) and fentanyl (2 µg/kg); vecuronium (0.16 mg/kg) was administered to facilitate tracheal intubation. Anesthesia was maintained with 50% nitrous oxide and 0.6 - 2.5% sevoflurane in oxygen. Sixty patients were randomly allocated into two groups of equal size using a computer-generated random number table, to receive either racemic ketamine (6 µg/kg/minute) or a similar volume of saline (placebo) immediately after orotracheal intubation continuing until wound closure. Ten minutes before wound closure, all patients received 5 mg of morphine. Following tracheal extubation, the patients were transferred to the post-anesthesia care unit (PACU).

For blinding, a nurse who was not involved in the evaluation of the patients prepared the study solutions and labeled on intraoperative infusion pump syringes. The same surgical team performed all surgeries. The attending physicians, patients, and all other personnel involved in the study were blinded to the treatment assignments.

Analgesia in the PACU was initially provided via titrating morphine in increments of 3 mg every 5 minutes until the VAS pain score was ≤ 3 cm. Patients were also given access to a PCA device set to deliver 1-mg boluses of intravenous (IV) morphine, with a lockout period of 5 minutes and no background infusion or limits. The PCA regimen was continued for 24 hours. As additional analgesia; all patients were ordered 1000 mg paracetamol intravenously, every 8 hours for 24 hours, to be administered. Patients received 4 mg ondansetron if they complained of nausea and vomiting.

Nurses were unaware of the study protocol, documented intraoperative and postoperative part of proforma, assessed the VAS score. They evaluated the patients using a modified Aldrete scoring system and recorded recovery time. Recovery time was defined as the time from the end of surgery until an Aldrete score = 10 (i.e., patient fully awake, oriented, and comfortable, with stable cardiovascular and respiratory signs).

Patients' level of pain at rest was assessed using a VAS at 1, 3, 6, 12, and 24 hours postsurgery. At the same times with VAS, the cumulative morphine consumption values were also recorded. Side effects during the first 24 hours postsurgery (e.g., nausea, vomiting, hallucinations, and double vision) were recorded.

Sample size was based on previously published data[8] which suggested that a minimum of 22 patients in each group were required to detect a 30% difference in cumulative 24-hour morphine consumption between the two groups, with a power of 90% at a level of significance of $p < 0.05$. To correct for possible excluded cases and deviation from normality, 30 patients were included in each group. Statistical analysis was performed using SPSS package for Windows, release 19.0.0 (IBM Corporation 2010, New York). Comparison of age, height, weight, duration of anesthesia, duration of surgery, recovery time, time to first morphine titration and morphine given by IV titration in PACU between two groups were normally distributed, the t-test was used. Gender, ASA and side effects were compared using Chi-square test. Cumulative morphine consumptions and VAS pain scores were analyzed by repeated-measures analysis of variance. Statistical significance was taken at a probability level of < 0.05.

RESULTS

A total of 60 subjects were randomized to group ketamine (n=30) or group control (placebo) (n=30, Figure 1). As shown in Table I, there were no significant differences in demographics (i.e. age, weight, height, and gender) or ASA status between the ketamine and

Table I: Patient characteristics*.

	Placebo Group**	Ketamine Group**	P***
Age (years)	58.8 ± 11.5	58.2 ± 9.58	0.347
Gender (male/female; n)	11/19	5/25	0.080
Height (cm)	165.26 ± 6.26	162.50 ± 5.58	0.264
Weight (kg)	79.83 ± 10.55	72.63 ± 14.77	0.056
ASA (I/II/III; n)	1/22/7	2/24/4	0.538
Duration of anesthesia (min)	135.33 ± 21.73	132.00 ± 19.72	0.584
Duration of surgery (min)	118.00 ± 19.14	117.50 ± 19.15	0.920
Recovery time (min)	59.50 ± 13.66	63.50 ± 11.07	0.218
Time to first morphine titration (min)	11.63 ± 3.21	22.73 ± 5.72	< 0.0001
Morphine given by IV titration in PACU (mg)	18.70 ± 3.75	10.50 ± 3.31	0.559

**Data present mean ± SD (standard deviation) or number of patients; **n = 30; ***p < 0.05 was considered statistically significant.*

Table II: Cumulative morphine consumption and VAS pain scores during the first 24 hours postsurgery*.

	Placebo Group**	Ketamine Group**
Cumulative morphine consumption (mg)		
At 1 h	24.26 ± 4.77	14.70 ± 10.77
At 3 h	41.63 ± 10.79	23.96 ± 13.12
At 6 h	55.76 ± 12.56	28.73 ± 11.88
At 12 h	70.60 ± 10.44	35.30 ± 10.64
At 24 h	85.20 ± 8.01	47.00 ± 15.30
VAS score (cm)		
At 1 h	3.46 ± 0.86	2.83 ± 1.20
At 3 h	2.86 ± 0.81	1.60 ± 0.81
At 6 h	2.10 ± 0.80	0.90 ± 0.66
At 12 h	1.40 ± 0.77	0.26 ± 0.44
At 24 h	0.63 ± 0.61	0.20 ± 0.48

**Values are expressed as mean ± SD; **n = 30*

Table III: Incidence of side effects in the two groups*.

	Placebo, n (%)	Ketamine, n (%)	P**
Nausea	14 (47)	7 (23)	0.058
Vomiting	5 (17)	1 (3)	0.195
Hallucinations	2 (7)	2 (7)	0.999
Double vision	8 (27)	4 (13)	0.333

**Values are expressed as number and percentage.*
***p < 0.05 is considered statistically significant.*

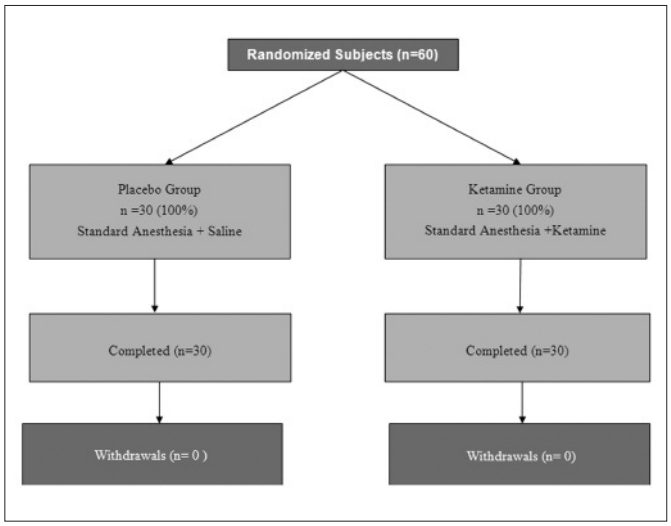

Figure 1: Subject disposition.

control groups. There were also no differences between the two groups in the duration of anesthesia and surgery. Recovery time was longer in the ketamine group (63.50 ± 11.07 minutes) than in the placebo group (59.50 ± 13.66 minutes). The difference was insignificant statistically (p = 0.268, Table I).

Postoperative cumulative morphine consumption was significantly less in the ketamine group than in the placebo group at 1, 3, 6, 12, and 24 hours postsurgery (p < 0.001, Table II). In the ketamine group, the time to first morphine titration was 22.73 ± 5.72 minutes, while it was 11.63 ± 3.21 minutes in the placebo with statistically significant difference (p < 0.001). The ketamine group required less morphine titration (10.50 ± 3.31 mg) than the placebo group (18.70 ± 3.75 mg), however, the difference was insignificant statistically (p = 0.559, Table I). Postoperative VAS scores at all measurement times were significantly less in the ketamine group than in the placebo group (p < 0.001, Table II).

Mean arterial pressure and heart rate did not differ significantly between the two groups during the perioperative period. Regarding adverse side effects, there were no statistically significant differences between the ketamine and placebo groups in nausea (23% vs. 47%), vomiting (3% vs. 17%), hallucinations (7% vs. 7%), or double vision (13% vs. 27%, Table III).

DISCUSSION

The main finding of the present study was that intraoperative, low-dose, continuous infusion of ketamine reduced pain and morphine consumption during the 24 hours immediately following knee replacement surgery. It also prolonged time to the first analgesic request. Morphine consumption was reduced by 45%.

Previous studies of ketamine have tested a range of doses and methods of administration. Those focused on intraoperative continuous IV ketamine infusion used doses of 1 - 10 µg/kg/hour, and reported reductions in morphine consumption of up to 55%.[8,10-17] The dosing schedule used in the present study differed from that of

others in which patients commonly received IV bolus ketamine before skin incision. Contrary to these, these patients did not receive bolus ketamine, and ketamine was not administered after surgery. However, we achieved the same analgesic effects as that of previous studies.[8,10-17]

Ketamine produces better postoperative pain relief than general or epidural anesthesia alone, when administered as a 0.5 mg/kg pre-incisional bolus with 0.2 mg/kg repeated at 20-minute intervals intraoperatively.[18] This suggests that administration of ketamine at repeated intervals may be as effective as continuous infusion. When ketamine is administered throughout a surgical procedure, either uninterrupted or at frequent intervals, less morphine is required during the early postoperative period. This may be due to ketamine's inhibitory effect on both peripheral and central sensitization.[7,19-22] In the present study, the infusion of ketamine initiated before incision and continued until wound closure may have prevented pathological pain. The pain-prevention mechanisms of ketamine are said to be the inhibition of sensitization of the nociceptive pathways, prevention of activation of the pronociceptive system associated with opiates, and prevention of opiate tolerance.[7,19-23] For the prevention of pathological pain, following severe tissue injury, such as during surgical procedures, ketamine should be administered for the duration of high-intensity noxious and inflammatory stimulation, not only during the initial trauma.[7,19-22]

A number of studies have been published on the analgesic effect of ketamine after orthopedic procedures. Minville *et al*. reported that pre-emptive use of ketamine was useful during orthopedic surgery in a mouse model for decreasing short- and long-term hyperalgesia, and also for enhancing the effectiveness of morphine, resulting in improved mobilization.[23] Recently, Perrin and Purcell reported the results of a pilot study on intraoperative ketamine infusion during knee arthroplasty under general and spinal anesthesia. They administered a ketamine bolus of 0.5 mg/kg followed by ketamine infusion of 4 µg/kg/minute, or equivalent volumes of the placebo saline solution. Infusion commenced before the surgical incision was made and continued until the surgical wound was bandaged. More patients were pain-free at 6 months postsurgery in the ketamine group than in the control group. In the present study, the patients also received general anesthesia together with ketamine infusion but the population was larger and pain was measured only within the first 24 hours of surgery; patients received neither spinal anesthesia nor ketamine bolus.

Remerand *et al*. evaluated ketamine's effect when combined with multimodal analgesia on postoperative pain following total hip arthroplasty.[11] They administered IV ketamine before incision (0.5 mg/kg) and 24 hours infusion (2 µg/kg/minute). Postoperative analgesia included IV acetaminophen and ketoprofen, plus morphine/droperidol PCA. They reported that the addition of ketamine decreased morphine consumption during the first 24 hours postsurgery by 28%. In contrast, in the present study neither bolus ketamine nor postoperative acetaminophen, ketoprofen, or droperidol were administered.

De Kock *et al*. investigated whether intraoperative subanesthetic doses of ketamine had a postoperative antihyperalgesic or analgesic effect, and compared the effectiveness of systemic vs. epidural administration.[10] Patients received an IV ketamine bolus dose of 0.5 mg/kg followed by infusion of 0.25 mg/kg/hour. The study found that hyperalgesia and the morphine PCA requirement were significantly reduced. Patients reported significantly less residual pain up to the sixth postoperative month. These observations support the theory that subanesthetic IV ketamine administered during anesthesia reduces wound hyperalgesia and is a useful adjuvant in perioperative balanced analgesia.

In the present study intraoperative low-dose ketamine infusion was not associated with significant side effects, which is similar to previous reports.[18]

Unfortunately, one limitation of the present study was that VAS scores were not recorded after the postoperative first 24 hours. In addition, the analgesic effect of ketamine on postoperative mobilization was not evaluated. These effects should be addressed in future studies.

CONCLUSION

Intraoperative continuous ketamine infusion reduced morphine consumption, and enhanced postoperative pain relief. It did not cause any serious side effects. As such, intraoperative ketamine infusion should be considered as an adjunct to opioids for pain management following knee replacement surgery.

REFERENCES

1. Ekstein MP, Weinbroum AA. Immediate postoperative pain in orthopedic patients is more intense and requires more analgesia than in post-laparotomy patients. *Pain Med* 2011; **12**:308-13.
2. Korean Knee Society. Guidelines for the management of postoperative pain after total knee arthroplasty. *Knee Surg Relat Res* 2012; **24**:201-7.
3. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001; **413**:203-10.
4. Kissin I. Pre-emptive analgesia. *Anesthesiology* 2000; **93**:138-43.
5. Carr DB, Goudas LC. Acute pain. *Lancet* 1999; **353**:2051-8.
6. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of pre-emptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* 2002; **96**:725-41.

7. Chizh BA. Low dose ketamine: a therapeutic and research tool to explore N-methyl-D-aspartate (NMDA) receptor-mediated plasticity in pain pathways. *J Psychopharmacol* 2007; **21**: 259-71.
8. Aveline C, Gautier JF, Vautier P, Cognet F, Hetet HL, Attali JY, *et al*. Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. *Eur J Pain* 2009; **13**: 613-9.
9. Colombani S, Kabbani Y, Mathoulin-Pelissier S, Gekiere JP, Dixmerias F, Monnin D, *et al*. Administration of ketamine during induction and maintenance of anaesthesia in postoperative pain prevention. *Ann Fr Anesth Reanim* 2008; **27**:202-7.
10. De Kock M, Lavad'homme P, Waterloos H. 'Balanced analgesia' in perioperative period: is there a place for ketamine? *Pain* 2001; **92**:373-8.
11. Remerand F, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L, *et al*. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg* 2009; **109**:1963-71.
12. Fu ES, Miguel R, Scharf JE. Pre-emptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. *Anesth Analg* 1997; **84**:1086-90.
13. Perrin SB, Purcell AN. Intraoperative ketamine may influence persistent pain following knee arthroplasty under combined general and spinal anaesthesia: a pilot study. *Anaesth Intensive Care* 2009; **37**:248-53.
14. Ilkjaer S, Nikolajsen L, Hansen TM, Wernberg M, Brennum J, Dahl JB. Effect of IV ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. *Br J Anaesth* 1998; **81**: 707-12.
15. Kararmaz A, Kaya S, Karaman H, Turhanoglu S, Ozyilmaz MA. Intraoperative intravenous ketamine in combination with epidural analgesia: postoperative analgesia after renal surgery. *Anesth Analg* 2003; **97**:1092-6.
16. Hadi BA, Al Ramadani R, Daas R, Naylor I, Zelko R. Remifentanil in combination with ketamine versus remifentanil in spinal fusion surgery: a double blind study. *Int J Clin Pharmacol Ther* 2010; **48**:542-8.
17. Adam F, Chauvin M, Manoir BD, Langlois M, Sessler D, Fletcher D. Small-dose ketamine infusion improves post-operative analgesia and rehabilitation after total knee arthroplasty. *Anesth Analg* 2005; **100**:475-80.
18. Argiriadaou H, Himmelseher S, Papagiannopoulou P, Georgiou M, Kanakoudis F, Giala M, *et al.* Improvement of pain treatment after major abdominal surgery by intravenous S(+)-ketamine. *Anesth Analg* 2004; **98**:1413-8.
19. Kissin I, Bright CA, Bradley EI Jr. The effect of ketamine on opioid-induced acute tolerance: can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? *Anesth Analg* 2000; **911**:1483-8.
20. Willert RP, Woolf CJ, Hobson AR, Delaney C, Thompson DG, Aziz G. The development and maintenance of human visceral pain hypersensitivity is dependent on the N-methyl-D-aspartate receptor. *Gastroenterology* 2004; **126**:683-92.
21. Celerier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, *et al*. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology* 2000; **92**: 465-72.
22. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. *Anesthesiology* 2005; **102**:211-20.
23. Minville V, Fourcade O, Girolami JP, Tack I. Opioid-induced hyperalgesia in a mice model of orthopaedic pain: preventive effect of ketamine. *Br J Anaesth* 2010; **104**:231-8.